

**REMARKS**

**Attached hereto is a marked-up version of the changes made to claim 1 by the current amendment. The attached page is captioned “Version with markings to show changes made.”**

Exemplary support for the amendment to the claim 1 can be found in the Specification at page 6, lines 14-18, page 9, lines 10-14 and lines 25-31, page 29, lines 14-20 and page 52, line 25 through page 53, line 11.

Claims 14 has previously been canceled without prejudice or disclaimer.

Claims 12 and 13 have been withdrawn from consideration.

Claims 1-11 with respect to SEQ ID NO:3 are under consideration in this application.

**Comments regarding restriction requirement**

Applicants reiterate the impropriety of the “restriction requirement” between SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 and SEQ ID NO:7 for reasons of record. Applicants expressly reserve the right to petition the restriction requirement if the full scope of the claims is not considered.

**Rejoinder of Method Claims**

Applicants reiterate that upon allowance of any product claim, there should be rejoinder of “method of use” claims 12-13, in accordance with the Commissioner’s Notice in the Official Gazette of March 26, 1996, entitled “Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b).”

**Scope of Enablement Rejection under 35 U.S.C. § 112, first paragraph**

Claims 1-2 and 9-11 were rejected under 35 U.S.C. § 112, first paragraph because the specification does not teach how to make and use the invention commensurate in scope with these claims. The Examiner alleges that:

- the Specification . . . does not reasonably provide enablement for an antibody to a “polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the full length of

the sequence of SEQ ID NO:3 wherein said naturally occurring amino acid sequence supports NADH dehydrogenase activity” (Office Action of January 31, 2003, at page 3).

- Applicant does not appear to have provided sufficient guidance with respect to “naturally-occurring” polypeptides and how to make and use antibodies to them. . . it is unpredictable that other “naturally-occurring” polypeptides having NADH dehydrogenase activity and at least 90% amino acid sequence identity to SEQ ID NO:3 exist (Office Action of January 31, 2003, at page 3).

The Office Action has asserted that the Specification does not enable a person of skill in the art to make and use the invention as claimed, i.e., “an isolated antibody which specifically binds to a “naturally-occurring” polypeptide having at least 90% identical to the full length of the sequence of SEQ ID NO:3 and having NADH dehydrogenase activity” irrespective of the particular form of the antibody (polyclonal, monoclonal, etc.)” (Office Action of January 31, 2003, page 4).

This is incorrect. Antibodies which specifically bind to a polypeptide can be made as long as that polypeptide, or fragments thereof, are available; there is no restriction on the amino acid sequence of polypeptides that can be used to make antibodies. Since a polypeptide having any amino acid sequence (including any amino acid sequence that is 90% identical to SEQ ID NO:3 and any naturally occurring amino acid sequence that is 90% identical to SEQ ID NO:3) can be used to make antibodies using the methods disclosed in the Specification, it is not necessary to identify particular naturally occurring amino acid sequences that are 90% identical to SEQ ID NO:3 that could be used in this manner.

The legal standard for enablement is a well-settled issue. For example, in *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (CAFC 1986), the court stated that:

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983), is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive...a patent need not teach, and preferably omits, what is well known in the art. *Lindemann*, 730 F.2d at 1463, 221 USPQ at 489.

The Specification discloses how to make both the polypeptides themselves and the antibodies which specifically bind the polypeptides.

**A. Making the Polypeptides**

The Specification fully enables the making of the SEQ ID NO:3 polypeptides. (See, e.g., Sequence Listing and Specification, page 14 line 10 through page 23, line 10.)

Applicants further submit that the Specification fully enables the making of the polypeptide variants to which the claimed antibodies specifically bind. The polypeptide sequence of SEQ ID NO:3 is provided in the Sequence Listing. The Examiner stated that:

Although the specification does provide some general guidance as to how to isolate other nucleic acids related to the nucleic acid encoding SEQ ID NO:3 and then test those polypeptides encoded by the related nucleic acids for NADH dehydrogenase function (e.g., pages 50-52), it is unpredictable that other “naturally-occurring” polypeptides having NADH dehydrogenase activity and at least 90% amino acid sequence identity to SEQ ID NO:3 exist. (Office Action mailed January 31, 2003, page 3.)

However, predictability of other “naturally-occurring” variant polypeptides is not needed in order to make such polypeptides. That is, the claims define the variant polypeptides as “naturally occurring” and being at least 90% identical to the amino acid sequence of SEQ ID NO:3. The existence of such variants is made by nature; and “naturally occurring” polypeptide variants occur in nature. The Specification teaches how to find polynucleotide variants (See, e.g., page 37, lines 20 through page 38, line 2) which can then be expressed to make polypeptide variants. The Specification also teaches how to use antibodies to purify naturally occurring NDS-2 (See, e.g., page 53, lines 13-23). The scope of the polypeptide variants to which the claimed antibodies specifically bind is described by the phrase “at least 90% identical to the full length of the sequence of SEQ ID NO:3.” The Specification describes how to use BLAST to determine whether a given sequence falls within the “at least 90% identical” scope (See, e.g., page 47, lines 14-29). In addition, determination of percentage identity is well known in the art. Moreover, the “comprising” language used to define the variant polypeptides does not preclude the ability to make the claimed subject matter. The term “comprising” as used in the Specification merely encompasses, for example, fusion proteins which contain the variant sequences (See, e.g., page 18, lines 15-21, page 20, lines 9-23, page 24, line 21

through page 25, line 11, and page 52, lines 3-15). Methods for making fusion proteins are well known in the art.

Applicants submit that the Specification fully enables the making of the immunogenic fragments of the SEQ ID NO:3 polypeptide to which the claimed antibodies specifically bind. The polypeptide sequence of SEQ ID NO:3 is provided in the Sequence Listing. Preparation of immunogenic fragments is described in the Specification, e.g., at page 29, lines 14-20 and page 52, line 25 through page 53, line 11.

Applicants note that the instant Specification states that ““immunologically active” refers to the capability of the natural, recombinant, or synthetic NDS, or any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.” ( page 6, lines 15-18.) The terms “immunologically active” and “immunogenic” are interchangeable. Prediction of immunogenic fragments may be done using methods described in the Specification, such as the use of DNASTAR software, as well as choosing possible epitopes near the C-terminus or in hydrophilic regions, e.g., on page 52, line 25 through page 53, line 3.

The ability of a given fragment to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies are tests for whether the fragment is “immunogenic” (See, e.g., page 6, lines 15-18, page 29, line 1 through page 30, line 23, page 36, line 17 through page 37, line 4, page 41, lines 1-19, and page 52, line 25 through page 53, line 3). The tests of fragments by these methods are routine practices in the art and, hence, do not require undue experimentation (In re Wands (858 F.2d 731, 8 USPQ2d 1400) Fed. Cir. 1988); the Specification provides a test for antibody binding (See, e.g., at page 30, lines 17-23).

#### **B. Making the Antibodies**

Applicants submit that the Specification fully enables the making of the claimed antibodies, (See, e.g., page 29, line 1 through page 30, line 23, and page 52, line 25 through page 53, line 11).

The Examiner asserts that the Specification allegedly provides insufficient guidance as to the making and using of “an antibody to a “naturally-occurring” polypeptide at least 90% identical to SEQ ID NO:3 and having NADH dehydrogenase activity as is encompassed by the full breadth of the claims

as currently recited, irrespective of the particular form of the antibody (polyclonal, monoclonal, etc.)” (Office Action mailed January 31, 2002, page 4). The Examiner concludes that “the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue with respect to other “naturally-occurring” polypeptides other than SEQ ID NO:3.” (Office Action mailed January 31, 2002, page 4.)

However, the Examiner is misreading these claims. The claims are directed to isolated antibodies which specifically bind to the recited polypeptide and no other polypeptide.

Further, the Examiner misapplies the law. To enable the claimed invention, Applicants need only disclose information sufficient to permit one of ordinary skill in the art to make and use the invention as claimed, without *undue* experimentation. It is the Examiner’s burden to establish that undue experimentation would be necessary to carry out Applicants’ invention. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

The Specification, e.g., at pages 29-30, describes methods well known in the art for making antibodies to the claimed polypeptides and polypeptide variants of the present invention. These methods include, but are not limited to, the production of monoclonal antibodies, polyclonal antibodies, chimeric antibodies, single chain antibodies, Fab fragments, F(ab’)<sub>2</sub> fragments, and fragments produced by a Fab expression library. With respect to monoclonal antibody production, the Specification describes a number of techniques known in the art for producing them, including the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. References detailing the particulars of those techniques are incorporated into Applicants’ Specification. Also, included in the disclosure are screening methods for identifying antibodies having the desired specificity.

In general, antibody production is an empiric process that necessarily requires immunization with particular putative immunogenic polypeptide sequences and subsequent screening of the products (See, e.g., antisera, hybridoma supernatants, recombinant immunoglobulin libraries or panels of highly specific binding reagents) to identify those fragments capable of giving rise to antibodies having the requisite specificity and affinity for the target antigen (in the present case, the SEQ ID NO:3 polypeptide and its variants) as defined by the claims. This procedure is routine in the art, and does not constitute undue experimentation which would render Applicants’ invention not enabled. See, e.g., *In re Wands*

8USPQ 2d 1400 (CAFC 1988). Indeed, the generation of antibodies necessarily involves genetic rearrangement in reaction to immunogenic challenge; that rearrangement process, and the resulting products, are inherently variable and constitute the basis for the remarkable ability of the mammalian immune system to respond to novel antigenic challenges with a high degree of specificity. Therefore, the process of challenge and screening are an inherent and unavoidable part of identifying immunogenic polypeptide sequences, and cannot be considered undue experimentation.

The Specification discloses methods to make antibodies which specifically bind to a polypeptide having any particular amino acid sequence (See, e.g., page 29, line 1 through page 30, line 23 and page 52, line 25 through page 53, line 11). Given the information provided by SEQ ID NO:3, one of skill in the art would be able to routinely obtain antibodies which specifically bind to “a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence SEQ ID NO:3 wherein said naturally occurring amino acid sequence supports NADH dehydrogenase activity.” For example, an animal could be immunized with a polypeptide having a particular naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:3, antibodies could be isolated from the animal, and the antibodies could be screened to identify antibodies which specifically bind to the recited polypeptide. Further, the Specification provides an assay for determining whether a particular variant of SEQ ID NO:3 possesses NADH dehydrogenase activity, (See, page 52, lines 16-23.

In sum, Applicants disclosure as filed discloses information sufficient to permit a skilled artisan to make the claimed antibodies and the polypeptides to which the claimed antibodies specifically bind. Accordingly, the Specification would allow one of skill in the art to practice the full scope of what is claimed.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first

paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the claimed antibodies and the polypeptides to which the claimed antibodies specifically bind. Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies and the polypeptides to which the claimed antibodies specifically bind.

Accordingly, the legal standard for enablement has been fulfilled and withdrawal of this rejection is in order.

**Written Description Rejection under 35 U.S.C. § 112, first paragraph**

Claims 1-2 and 9-11 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that:

- Applicant does not appear to have provided a description of which polypeptide sequences are “naturally-occurring,” even among those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO:3. Neither does Applicant appear to have provided a description of how the structure of the polypeptide of SEQ ID NO:3 relates to the structure of other “naturally-occurring” polypeptides which have NADH dehydrogenase activity, even for those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO:3. (Office Action of January 31, 2003, at page 4).
- Since Applicant does not appear to have been in possession of the genus of polypeptides to which the instantly recited antibody specifically binds; Applicant in turn does not appear to be in possession of the genus of antibodies specifically binding these polypeptides. (Office Action of January 31, 2003, at page 5).

This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

. . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

. . . Mention of representative compounds encompassed by generic claim language *clearly is not required by Section 112 or any other provision of the statute*. But, where no explicit description of a generic invention is to be found in the specification...mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

. . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, *it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by ‘other appropriate language.’* *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

Attention is also drawn to the Patent and Trademark Office’s own “Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1”, published January 5, 2001, which provide that :

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics<sup>42</sup> which provide evidence that applicant was in possession of the claimed invention,<sup>43</sup> i.e., *complete or partial structure*, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.<sup>44</sup> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.<sup>45</sup> *If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.*<sup>46</sup> [emphasis added]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

**I. The Specification provides an adequate written description of the claimed antibodies which specifically bind the claimed “variants” of SEQ ID NO:1**

The subject matter encompassed by claims 1-2 and 9-11 is disclosed by the Specification, conventional and well known to one skilled in the art.

Independent claim 1 recites in the preamble “[A]n isolated antibody which specifically binds to a polypeptide” said polypeptide selected from the group consisting of: . . . b) a polypeptide that is i) “a naturally occurring amino acid sequence” that is ii) “at least 90% identical to the full length of the sequence of . . . SEQ ID NO:3” and iii) “wherein said naturally-occurring amino acid sequence supports NADH dehydrogenase activity.” The Examiner’s position is based upon the theory that the Specification provides an adequate written description of SEQ ID NO:3 and an antibody to SEQ ID NO:3 or immunogenic fragments thereof, however, the Specification allegedly lacks an adequate written description of the variant polypeptides because, “neither the common attributes of the genus nor the identifying attributes of individual species other than SEQ ID NO:3 appear to have been described” (Office Action of January 31, 2003 at pages 4-5). Applicants strongly disagree with this position.

Such a position ignores that the polypeptides recited in claim 1 b) *are* described in terms of their structure which in turn describes the characteristics of the antibodies which specifically bind the polypeptides. That is, the claimed antibodies specifically bind to the claimed polypeptides which are ***“at least 90% identical to the full length of the sequence of SEQ ID NO:3.”*** The structure of SEQ ID NO:3 is provided in the Specification, for example, at page 3 of the Sequence Listing and Figures 2 and 6 for SEQ ID NO:3. The phrases “percent identity” or “% identity” as well as methods for determining such identity are well known to the skilled artisan. A definition of polypeptide “variants,” the types of amino acid changes and substitutions that may be made while still retaining biological or immunological activity, and computer programs well known in the art which provide guidance in identifying such variants may be found, for example, on page 5, line 29 through page 6, line 6. A detailed description of the chemical and structural features of SEQ ID NO:3 which contribute to the characterization of SEQ ID NO:3 and other related proteins associated with NADH dehydrogenase subunits are provided (See, e.g., page 12, line 28 through page 13, line 5 and Figures 6 and 10). Ninety percent variants of the claimed polypeptides are described (See, e.g., page 14, lines 5-9).

Methods of making antibodies and detection of antigenic regions used to make antibodies is provided throughout the Specification (See, e.g., page 9, lines 25-31; page 29, line 26 through page 30, line 23; and Example X, pages 52-53).

Furthermore, claim 1 recites not only that the polypeptide “variants” are those variants at least 90% identical to the full length of the sequence of SEQ ID NO:3, but also have “*a naturally occurring amino acid sequence.*” Through the process of natural selection, nature will have determined the appropriate polypeptide sequences. Given the information provided by SEQ ID NO:3 (the amino acid sequence of NDS-2) and SEQ ID NO:4 (the polynucleotide sequence encoding NDS-2), one of skill in the art would be able to routinely obtain “a naturally-occurring amino acid sequence at least 90% identical to the full length of the sequence of SEQ ID NO:3” as recited in claim 1. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application (See, e.g., page 37, lines 12-19; and Example VI at pages 50-51). Thus, one skilled in the art need not make and test vast numbers of polynucleotide sequences that are based on the amino acid sequence of SEQ ID NO:3. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. Moreover, once a candidate polypeptide is identified, its activity can be tested, such as using the assay as set forth in Example IX, page 52.

Nowhere in the Office Action of January 31, 2003, does the Examiner offer any evidence that one of ordinary skill in the art would not have understood from the disclosure in the Specification along with “[w]hat is conventional or well known to one of ordinary skill in the art,” that Applicants were in possession of both the claimed antibodies which specifically bind to the claimed proteins and to the claimed proteins at least 90% identical to the full length of the sequence of SEQ ID NO:3, wherein said naturally-occurring amino acid sequence supports NADH dehydrogenase activity.

When provided with the detailed description as noted above, one of ordinary skill in the art “would have understood the inventor to be in possession of the claimed invention at the time of filing.” That is, one of ordinary skill in the art would recognize **antibodies** that specifically bind to polypeptide

sequences which are variants at least 90% identical to the full length of the sequence of SEQ ID NO:3 as well as recognize **polypeptide sequences** which are variants at least 90% identical to the full length of the sequence of SEQ ID NO:3. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:3 and to determine the % identity to SEQ ID NO:3 of the variant. Likewise, antibodies which specifically bind to such variant polypeptides would also be recognized by one of skill in the art. Accordingly, the Specification provides an adequate written description of the recited variants of SEQ ID NO:3 and the antibodies which specifically bind said variants.

## II. The Specification provides an adequate written description as required by law

Applicants submit that case law in the area of the written description requirement of 35 U.S.C. 112, first paragraph is clear with regard to the details considered sufficient to describe a claimed genus:

. . . Mention of representative compounds encompassed by generic claim language *clearly is not required by Section 112 or any other provision of the statute*. But, where no explicit description of a generic invention is to be found in the specification . . . mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

. . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, *it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'* *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

The Specification sets forth a description of the claimed polypeptide variants using "other appropriate language" as indicated above in connection with the remarks regarding "a naturally-occurring amino acid sequence at least 90% identical to the full length of the sequence of SEQ ID NO:3." The claimed variants have been described in terms of their relationship to the chemical structure of SEQ ID NO:3 and structural requirements (See, e.g., page 3 of the Sequence Listing; Figures 2, 6 and 10; and page 12, line 28 through page 13, line 5). The Specification provides a means

of identifying naturally occurring functional variants having 90% sequence identity with SEQ ID NO:3 (See, e.g., page 11, lines 23-29; page 37, lines 12-19; Example VI at pages. 50-51; and Example IX on page 52. Applicants therefore submit that the “genus is sufficiently identified in [the instant] application by ‘other appropriate language’” as stated in *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960).

Additionally, the Specification sets forth a description of the claimed antibodies to the variant polypeptides as described above in relation to the remarks addressing “an isolated antibody which specifically binds to a polypeptide.” The Specification provides methods of making antibodies and detection of antigenic regions used to make antibodies (See, e.g., page 9, lines 25-31; page 29, line 26 through page 30, line 23; and Example X, pages 52-53).

Applicants submit that “a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing” as stated in the Patent and Trademark Office’s own “Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1”, published January 5, 2001. Accordingly, claims 1-2 and 9-11 meet the statutory requirements for written description under 35 U.S.C. 112, first paragraph.

### **III. Conclusion**

The Office Action failed to base its written description inquiry “on whatever is now claimed.” Consequently, the Action did not provide an appropriate analysis of the present claims in view of their scope. In particular, the subject matter of the claims of the instant application is defined in terms of the chemical structure of SEQ ID NO:3. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides and the antibodies which specifically bind to such polypeptides as defined by the present claims is adequately described, as evidenced by specific passages of the Specification as set forth above. Furthermore, the Examiner has applied to the subject application a written description standard that has no basis in the law.

For at least the above reasons it is believed that claims 1-2 and 9-11 meet the written description requirement of 35 U.S.C. § 112, first paragraph. It is therefore requested that this rejection be reversed.

**Anticipation and Obviousness Rejections under 35 U.S.C. § 102 and § 103**

Claims 1 and 4 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bentlage et al. (Biochimica Biophysica Acta, 1234:63-73, 1995). In addition, a 35 U.S.C. § 103(a) rejection of claims 1-11 was applied over the combination of Walker et al. (J. Mol. Biol., 226:1051-1072, 1992) in view of Bentlage et al. (Biochimica Biophysica Acta 1234:63-73, 1995) and Ramakrishnan et al (U.S. Patent No. 5, 817,310). These rejections are traversed.

The present claims recite an antibody which **specifically binds** to a polypeptide comprising, *inter alia*, the amino acid sequence of SEQ ID NO:3 and “naturally occurring 90% variants” of SEQ ID NO:3 having NADH dehydrogenase activity. Thus, the antibody encompassed by the claims specifically binds the recited polypeptides and not other polypeptides.

The Specification teaches that the antibodies of claims 1 and 4 specifically bind to a polypeptide of SEQ ID NO:3 and a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the full length of the sequence of SEQ ID NO:3 having NADH dehydrogenase activity. “Specific binding” or “specifically binding” is defined in the Specification at page 10, lines 1-7:

The terms “specific binding” or “specifically binding,” as used herein, in reference to the interaction of an antibody and a protein or peptide, mean that the interaction is dependent upon the presence of a particular structure (i.e., the antigenic determinant or epitope) on the protein; in other words, ***the antibody is recognizing and binding to a specific protein structure rather than to proteins in general.*** For example, if an antibody is specific for epitope “A”, the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled “A” and the antibody will reduce the amount of labeled A bound to the antibody.

The words of a claim must be given their “plain meaning” unless applicant has provided a clear definition in the Specification, since Applicants can be their own lexicographer (MPEP §2111.01). Applicants’ use of a term is determined by the Applicants and does not require the use to be consistent “with the

well-known and art-recognized specificity of antibody interaction with epitopes” as the Examiner would require (Office Action of March 21, 2002, page 5). In light of the definition provided in the Specification, claims 1 and 4 mean that the claimed antibody and its interaction with a particular structure leads to “recognizing and binding to a specific protein structure rather than to proteins in general,” i.e., the polypeptide of SEQ ID NO:3 and naturally occurring polypeptides 90% identical to the full length sequence of SEQ ID NO:3 having NADH dehydrogenase activity.

The Office Action of January 31, 2003 further alleges that Bentlage et al. “teach an antibody that based upon the evidence provided in Bentlage et al., appears to bind the instantly recited polypeptide of SEQ ID NO:3” (page 6). Bentlage et al. teach the use of a bovine polyclonal antibody produced in response to exposure to bovine multi-polypeptide Complex I antigen, a holo-enzyme. The bovine Complex I antibody is also taught by Bentlage et al. in Figure 4a to bind to about 10 human Complex I subunits which Bentlage et al. describe as “probably all encoded in nDNA (nuclear DNA; Bentlage et al. page 70, first paragraph, column 1). Clearly, the skilled artisan can infer that Bentlage et al. “presume” that the bovine Complex I antibody detects nDNA because

Antibodies against Complex I subunits with skeletal mitochondrial proteins from myopathy patients showed a generalized reduction of all cross-reacting polypeptides, in some cases with a disproportionate and severe deficiency of a few subunits [1,6]. *The ND subunits [encoded by the mitochondrial genome] were not detected by these antibodies* (Bentlage et al. page 63, first paragraph, column 2, emphasis added).

The Office Action concludes that “SEQ ID NO:3 would be an inherent property of the polypeptide recognized” (Office Action of January 31, 2003, page 6). Applicants respectfully submit that the “arrows” of Figure 4a allegedly represent 10 subunits of Complex I. The subunits are confirmed to be neither nDNA encoded nor ND encoded, and no specific molecular mass is associated with any of the 10 subunits. Further, Bentlage et al. did not teach which Complex I subunits the holo-enzyme antibody detected in bovine Complex I.

Examination of a recent BLASTP analysis of SEQ ID NO:3 against the Genpept database (version 134, NCBI) establishes SEQ ID NO:3 as the Complex I subunit known as NDUF4 (results enclosed). Upon closer examination of some 35 nuclear-encoded human Complex I protein subunits,

there are at least six subunits of comparable amino acid sequence length or molecular mass (kD) as SEQ ID NO:3:

<u>Subunit</u>	<u>Length</u>	<u>Size in kD</u>	<u>GenBank Accession No.</u>
NDUFS5	106 amino acids	15 kD	O43920
NDUFA6	128 amino acids	14 kD	AF047182
NDUFA7	113 amino acids	14.5 kD	O95182
<b>NDUFB4</b>	<b>129 amino acids</b>	<b>15 kD</b>	<b>NP_004583 (SEQ ID NO:3)</b>
NDUFB5	189 amino acids	16 kD	NP_002483
NDUFB6	128 amino acids	17 kD	NP_002484
NDUFB7	137 amino acids	18 kD	NP_004137
NDUFC2	119 amino acids	14.5 kD	NP_004540

(Loeffen et al. Biochem. Biophys. Res. Comm. (1998) 253:415-422, p. 416, of record; J. Smeitink and L. van den Heuvel, Am. J. Hum. Genet. (1999) 64:1505-1510, enclosed herewith)

The Office Action asserts that "[S]EQ ID NO:3 would be an inherent property of the polypeptide recognized." With respect to Bentlage et al., the Office Action states that the rejection, "does not necessarily rely on the fact that an antibody may specifically bind more than one polypeptide that shares the epitope recognized by the antibody . . . Bentlage et al. teach an antibody that based upon the evidence provided in Bentlage et al., appears to bind the instantly recited polypeptide of SEQ ID NO:3." (Office Action of January 31, 2003, page 6.) Applicants strongly disagree with such a conclusion and invite the Office to show where it is taught that this 15 kD Complex I subunit is NDUFB4 and not one of the other 15 kD Complex I subunits.

At the time of the Bentlage paper, the human Complex I enzyme subunits consisting of NDUFA3, -7, -10, NDUFB2, -4 (SEQ ID NO:3), -8, and -10 (NDUFC2 had not yet been sequenced) (Loeffen et al. p. 416). Hence, what is readily apparent to one of skill in the art upon examination of Figure 4a is that it is impossible to determine which, if any, of the seven subunits described *supra*, were actually detected, let alone that the bovine polyclonal antibody had specifically bound SEQ ID NO:3. Presumptions asserted by the Office to the contrary are without scientific evidence and not supported by Bentlage et al. Thus, of the 42 known Complex I subunits (seven being ND subunits) in humans, potentially only 10/35 nuclear encoded subunits might be detected by the

bovine antibody to the holo-enzyme. However, which subunits were detected by the holo-enzyme antibody were not known at the time of Bentlage et al.

Further, Applicants note that the claims do not recite an antibody which binds specifically to an epitope of a polypeptide, but rather an antibody which binds specifically to a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or to a naturally occurring polypeptide variant of SEQ ID NO:3 having at least 90% sequence identity and NADH dehydrogenase activity. The interaction of the antibody and the recited polypeptides is dependent on the epitope bound by the antibody, but that does not mean that an antibody that binds specifically to an epitope on the recited polypeptide is the same thing as an antibody that binds specifically to the recited polypeptide. The antibodies recited by the claims bind specifically to the recited polypeptides. Bentlage et al. provide no recognition of such an antibody.

Thus, the Examiner has failed to provide a *prima facie* case for anticipation of SEQ ID NO:3. It would appear that the Examiner may be using "hindsight reconstruction" in making a broad and sweeping conclusion that an "arrow" designating a "result not shown" in the gel of Figure 4a in the Bentlage et al. paper is particular to SEQ ID NO:3. Applicants remind the Examiner that SEQ ID NO:3 is a novel sequence that was not yet disclosed at the time that Bentlage et al was published; and that Bentlage et al. provide no recognition of SEQ ID NO:3. Applicants have provided evidence that there are at least seven nuclear encoded Complex I subunits having similar lengths and/or migration patterns based on molecular weight which may be represented by an "arrow" on the SDS-PAGE gel of Figure 4a. Clearly, the skilled artisan would conclude that the holo-enzyme antibody has at best a 1 out of 7 possibility of detecting SEQ ID NO:3, but not that it conclusively does so. Consequently, the polyclonal antibody of bovine Complex I can neither be anticipated to specifically bind SEQ ID NO:3 nor provide to one of skill in the art the *prima facie* expectation that such binding would occur. Therefore, claims 1 and 4 are not anticipated by the teachings of Bentlage et al. Withdrawal of this rejection based on 35 U.S.C. §102(b) is therefore requested.

Walker et al. does not make up for the deficiencies of Bentlage et al. Walker et al. describe a bovine B15 sequence of NADH:ubiquinone oxidoreductase which has some sequence similarity to SEQ ID NO:3. Again, the Office Action relies on the previously discussed limitation of "specifically

binds” to assert that the polypeptide taught by Walker et al. which allegedly has “numerous shared epitopes” with SEQ ID NO:3 would also “specifically bind” to the claimed antibody. The Office Action provides no evidence of what “shared epitopes” exist between SEQ ID NO:3 and the B15 polypeptide of Walker et al.; and Walker et al. do not teach epitopes of bovine B15. The B15 polypeptide of Walker et al. is alleged by the Office Action to have 75.8% identity with SEQ ID NO:3. The claimed invention includes “a naturally-occurring amino acid sequence at least 90% identical to the full length of the sequence of SEQ ID NO:3, said naturally occurring amino acid sequence having NADH dehydrogenase activity.” Clearly, the sequence taught by Walker et al. is less than 90% identical to SEQ ID NO:3 and is not encompassed by the claimed invention.

The Office’s broad sweeping conclusion is based on the collective teachings of Bentlage et al., Walker et al. and Ramakrishnan et al. that the “ordinary artisan at the time the invention was made knew that antibodies produced to either bovine Complex I polypeptides, or fragments thereof, would specifically bind the corresponding human Complex I polypeptide of SEQ ID NO:3.” (Office Action of January 31, 2003, page 8.). This argument fails on several points.

First, the sequence of Walker et al. is not SEQ ID NO:3, and the antibodies of the claimed invention bind *inter alia*, to SEQ ID NO:3, a polypeptide not taught by Walker et al. or Bentlage et al.

Secondly, Bentlage et al. teach that bovine complex I antibodies bind only *some* human Complex I polypeptides, not all, and *none of the human subunit polypeptides which might be bound by the bovine Complex I antibody are identified*. The Office’s presumption that SEQ ID NO:3 would be so bound appears to be “hindsight reconstruction”, *supra*.

Thirdly, Ramakrishnan et al. describes various methods for producing antibodies, but has no information at all relating to SEQ ID NO:3. Walker et al. and Bentlage et al. teach also fail to teach SEQ ID NO:3. Accordingly, the combination of those three documents would not have guided one skilled in this art to the claimed subject matter.

Thus, Bentlage et al., Walker et al. and Ramakrishnan et al. do not provide a *prima facie* case for obviousness of the claimed invention. Therefore, withdrawal of the rejection based on 35 U.S.C. §103(a) is respectfully requested

**CONCLUSION**

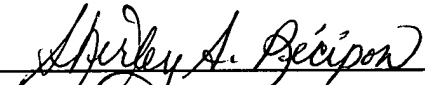
In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

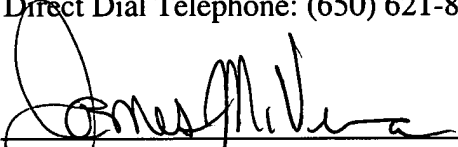
Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

Respectfully submitted,  
INCYTE CORPORATION

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Enclosures:

1. J. Smeitink and L. van den Heuvel, Am. J. Hum. Genet. (1999) 64:1505-1510
2. BLAST report showing the alignment of SEQ ID NO:3 with NDUFB4
3. GenBank file for AAD05421 (GI 4164446, NDUFB4)

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

Claim 1 has been amended as follows:

1. **(Four Times Amended)** An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:
  - a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, [and]
  - b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the full length of the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, wherein said naturally-occurring amino acid sequence supports NADH dehydrogenase activity[.] , and
  - c) an immunogenic fragment of a polypeptide consisting of at least 10 contiguous amino acid residues of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.